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PhRMA

January 3, 2005

Dockets Management Branch (HFA - 305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket Number 2004D-0440; Draft Guidance for Industry on Computerized Systems Used in Clinical Trials; 69 Federal Register 59239

Dear Sir/Madam:

The following comments on the above draft guidance are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2003, our members invested over $32 billion in the discovery and development of new medicines.

General Comments
While the word "should" is used throughout the Guidance document (per lines 35-36), the word "must" is also used in the document. PhRMA recommends that all instances of "must" be reviewed to ensure that these are requirements per predicate rules and that the word "must" be so defined.

II. BACKGROUND
The list of references in lines 41-43 is incomplete. PhRMA recommends not referencing specific regulations. For example, 21 CFR parts 50, 54, 56, 314, 601 and 814 are not mentioned.

Although lines 52-57 describe which computerized systems are in scope, it is unclear whether the Agency intends for this Guidance document to be applicable to computerized systems used at clinical sites to collect data where these systems are not under the control of either the sponsor or the investigator (e.g., hospital computer systems). PhRMA recommends that the Agency clarify in the Guidance document that these computerized systems are out of scope.

In addition, PhRMA recommends that the Guidance document explicitly state that sponsors are responsible for validating computer systems that they develop and provide to clinical investigators, while clinical investigators are responsible for validating computer systems that they develop. Although lines 350-354 speak to this distinction, this delineation of responsibilities should be made more explicit at the beginning of the document.

The expression of confidence in computerized system data used in lines 57-58, "... should have confidence that the data are no less reliable than data in paper form" is written in a negative manner and would be clearer if expressed in the manner used in lines 87-88; that is, "... *are*

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met with the same degree of confidence as is provided with paper systems."

III. GENERAL PRINCIPLES

Lines 76-77 state, "We recommend that each study protocol identify at which steps a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit data." PhRMA does not believe that the protocol is an appropriate document to present this information. It would be extremely difficult for the sponsor to know at the time the protocol is written at which steps a computerized system will be used across all investigator sites that will be involved in the study. PhRMA assumes the "steps" that are to be documented are general steps, but if this is not true, please clarify. PhRMA proposes that this recommendation be reworded as follows: "*We recommend that study or site records identify at which steps a computerized system were used to create, modify, maintain, archive, retrieve, or transmit data.*"

Lines 78-80 state, "For each study, we recommend that documentation identify what software and hardware are to be used in computerized systems that create, modify, maintain, archive, retrieve, or transmit data". PhRMA recommends that such documentation be limited to software and that the word "hardware" be deleted.

Lines 102-104 state "An audit trail that is electronic or consists of other physical, logical, or procedural security measures to ensure that only authorized additions, deletions, or alterations of information in the electronic record have occurred may be needed to facilitate compliance with applicable records regulations". An audit trail can neither authorize nor prevent additions, deletions or alterations of electronic records. PhRMA recommends that this sentence be reworded as follows: "*To facilitate compliance with applicable records regulations, an audit trail may be needed. It can be electronic or it can consist of other physical, logical or procedural security measures that ensure that all additions, deletions, or alterations of information in the electronic record have been recorded.*"

Lines 107-109 state that audit trails should also include <u>why</u> changes were made to the electronic record. The requirement to record why changes were made is a predicate rule requirement in Part 58 but not in the GCP regulations. Therefore, PhRMA suggests that this recommendation be reworded as follows: "*what the changes are, who made the changes and when the changes were made*".

V. STANDARD OPERATING PROCEDURES

Lines140-146 list SOPs that the Agency recommends be established. We believe that some of the SOPs listed are more appropriately addressed in plans, user manuals or other controlled documents. PhRMA therefore suggests that lines 137-138 be reworded as follows: "*We recommend that controlled documents (e.g., standard operating procedures (SOPs), plans or user manuals) pertinent to the use of the computerized system be available*".

Line 138 states that the documents should be available "on site". PhRMA suggests that the study site maintain only the SOPs (or other controlled documents) for functions that the investigator site performs. As an example, if the investigator is not responsible for change control, then the SOP on change control does not need to be available at the investigator site.

Lines 143 and 146 mention "contingency plans" and "alternative recording methods". These phrases appear to be synonymous. PhRMA requests that these terms, if different, be clarified.

VII. SYSTEM FEATURES
Lines 278-280 state, "It is not necessary to reprocess data from a study that can be fully reconstructed from available documentation. Therefore, actual application software, operating systems, and software development tools involved in processing of data or records do not need to be retained". PhRMA recommends that the phrase "*computer hardware*" be added to the list.

IX. SYSTEM DEPENDABILITY
Lines 385-392 address validation requirements for off-the-shelf software and the recommendations are consistent with those outlined in section 6.3 of the Agency's Guidance on General Principles of Software Validation. However, the recommendations in lines 401-409 of this Guidance document contradict lines 385-392. PhRMA recommends that lines 401-409 be deleted.

XII. COPIES OF RECORDS AND RECORDS INSPECTION
Lines 489-492 state, "Regardless of the method used to produce copies of electronic records, it is important that the copying process used produces copies that preserve the content and meaning of the record. For example, if you have the ability to search, sort, or trend records, copies given to FDA should provide the same capability if it is reasonable and technically feasible". PhRMA recommends that the phrase "For example" be deleted and that the second sentence begin with "*If you have the ability ...*".

DEFINITIONS
Some terms are not defined (e.g., site, firm). In addition, some definitions are not consistent with the text (e.g., audit trails). Furthermore, it is not clear why some terms are italicized. PhRMA recommends that terms used in the document be defined, that definitions be reviewed to ensure that they are consistent with the text, and that the intent of terms and phrases that appear in italics be clarified.

PhRMA appreciates the opportunity to submit these comments.

Sincerely,